New Approach to Ttreatment of Type II Diabetes – SGLT2 Inhibitors

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Introduction :

Type II Diabetes is attaining epidemic proportions across the globe.Many clinical trials have correlated the complications of diabetes: both macrovascular and microvascular,with degree of Glycaemic control. Guidelines recommend a target glycosylated haemoglobin (HbA_{1c}) of 7% or less, but a large number of patients fail to meet this target and, as of yet, no ideal pharmacological blood glucose-lowering agent exists. Hence the search for new antidiabetic drug continues.

Treatment with traditional glucose-lowering therapies, including metformin, sulphonylureas and insulin, is commonly limited by gastrointestinal side effects, weight gain and hypoglycaemia[1,2] .Treatment with thiazolidinediones has been associated with cardiovascular safety concerns, weight gain, increased fracture risk and fluid retention.[3,4] Dipeptidylpeptidase-4 (DPP-4) inhibitors are well tolerated, but are merely weight neutral. Glucagon-like peptide-1 (GLP-1) analogues result in moderate weight loss, but they need to be injected and their use is limited by gastrointestinal side effects.[5] The increasing prevalence of type 2 diabetes, in combination with limitations of current therapies, has led to the search for newer alternatives. SGLT2 inhibitors represent a novel 'glucuretic' therapeutic strategy for the treatment of type 2 diabetes, and are currently in phase III trials.

SGLT2 inhibitors inhibit glucose re-absorption in the proximal renal tubules providing an insulin independent mechanism to lower blood glucose. Their use in clinical practice is associated with improved glycaemic control, weight loss and a low risk of hypoglycaemia. Phase III cardiovascular safety studies are ongoing [6] .

Historical perspective :

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Phlorizin, a naturally occurring b-glucoside isolated from the bark of apple trees in 1835, was the first known SGLT inhibitor [7] .It acts as a potent non-selective competitive inhibitor of both SGLT1 and SGLT2. Administration of phlorizin caused glycosuria in rats, which normalized both the fasting and fed plasma glucose levels and completely reversed insulin resistance. However, it was not developed further because of its non-selective SGLT inhibition and low oral bioavailability,resulting from rapid in-vivo b-glucosidase-mediated intestinal degradation[7]. Sergiflozin and remigliflozin, the potent SGLT2 inhibitors subsequently synthesized, were tested in preclinical and clinical studies. All of these are phlorizin derivatives that are structurally modified to increase SGLT2 selectivity and improve oral bioavailability. Both these drugs were progressed to phase 1 clinical testing, but their further development was not pursued because of their unfavourable pharmacokinetic profile[8]. These drugs contained O-glucoside linkages that made them susceptible to hydrolysis by intestinal b-glucosidase, thus reducing their plasma halflife. Several specific SGLT2 inhibitors are currently under development including

1. dapagliflozin, - 7 clinical trials
2. canagliflozin, - 1 clinical trial
3. empagliflozin,
4. ipragliflozin and
5. tofogliflozin.
6. Remogliflozin Etabonate is a novel SGLT2 inhibitor (60-fold selective over SGLT1) that was shown to be effective in the Zucker diabetic fatty (ZDF) rat model of type 2 diabetes. Data presented showed short-term normalization of blood glucose during an oral glucose tolerance test at the highest doses used (10 mg/kg/day). It will be interesting to see whether this drug lives up to its promise in clinical trials [9].

These work independently of insulin to prevent glucose re-absorption from the glomerular filtrate resulting in a reduced renal threshold for glucose, glycosuria and net

calorie loss [10]. Dapagliflozin (developed by Bristol – Myers Squibb and AstraZeneca) is the furthest advanced compound in clinical development belonging to the SGLT2 inhibitor class.

Structure

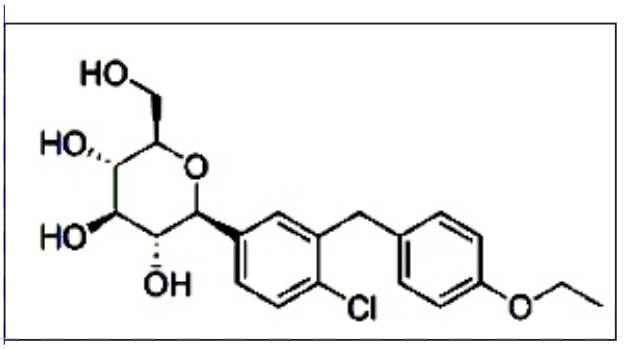
SGLT1 is expressed in the intestinal mucosa as well as the kidney. Its use as a therapeutic target is limited by side effects from malabsorption of glucose and galactose in the small intestine.[8] SGLT2 are expressed selectively in the kidney and they are upregulated in diabetic patients. The difference between SGLT1 and SGLT2 is shown in following table (Table No.1)

Table 1 : Comparison of SGLT1 and SGLT2 [11]

	SGLT1	SGLT2
• Site	Mainly intestine, other sites include brain, skeletal and heart muscle, liver, lungs, kidneys	Kidney
• Gene encoding	SLC5A1	SLC5A2
• Substrate	Glucose or galactose	Glucose
• Affinity for glucose	High	Low
• Capacity for glucose transport	Low	High
• Main function	Dietary glucose absorption	Renal glucose reabsorption
• Renal location	Late proximal straight tubule (S3)	Early proximal convoluted tubule (S1 &S2)
• Percentage of renal Glucose Reabsorption	10%	90%
• Mutation of encoding gene	Glucose/galactose malabsorption, leading to fatal diarrhoea*	Familial renal glucosuria, a benign condition
• Inhibitors of Transporter	Selective SGLT1 inhibitors: KGA2727 (Kessei Pharmaceutical Co. Ltd) advanced inclinical trials GSK1614235/ KGA3235 (Kissei Pharmaceuticals Co. Ltd, GlaxoSmithKline plc)	Dapagliflozin, canagliflozin, empagliflozin

*The gastrointestinal side effects have not been reported in clinical studies. SGLT1, sodium glucose co-transporter 1; SGLT2, sodium glucose co-transporter 2; SLC, solute carrier family.

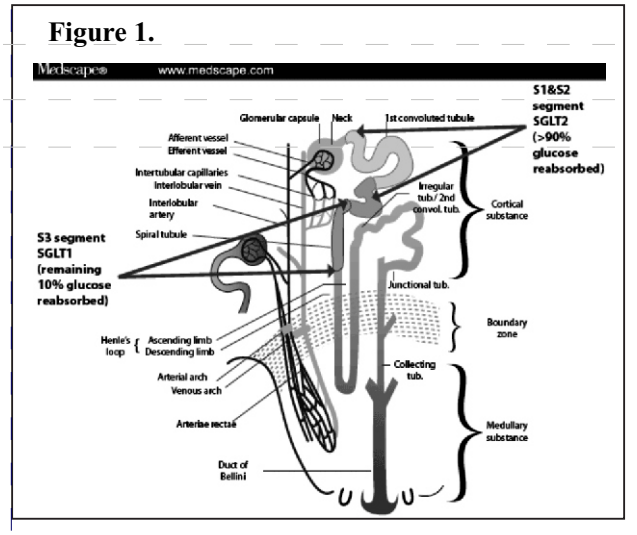
Dapagliflozin : Chemical structure - $C_{21}H_{25}ClO_6$



Mechanism of action

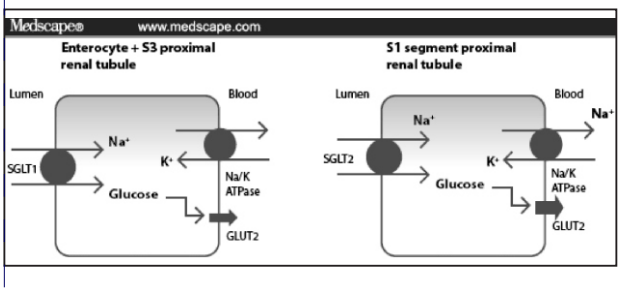
The renal system plays a very important role in glucose homeostasis. In the kidney, glucose is freely filtered at the glomerulus and is reabsorbed via active transport mechanisms in the proximal convoluted tubule. Two sodium-glucose co-transporters are responsible for glucose reabsorption: SGLT1 and SGLT2. SGLT1, which is also found in the gut and other tissues, accounts for about 10% of reabsorption. SGLT2, expressed exclusively in the S1 segment of the proximal tubule, accounts for about 90% of reabsorption (Figure 1).

Figure 1. Sites of glucose reabsorption in the S1, S2, and S3 segments of proximal tubules [9]



Glomeruli filter about 144 gm of glucose per 24 hours, nearly 100% of which is reabsorbed in the renal tubules. Glycosuria develops when the blood glucose level reaches the renal threshold for reabsorption,which is about 8–10 mmol/l (180 mg/dl.Renal tubular reabsorption is known to undergo adaptations in uncontrolled diabetes. There is an up-regulation of both GLUT2 and SGLT2 in diabetes to maintain renal tubular glucose reabsorption. SGLT2 mRNA expression is up-regulated in the kidneys of diabetic rats, and reversed by lowering blood glucose levels. In comparison to the cells of healthy individuals, the exfoliated proximal tubular epithelial cells from the fresh urine of diabetic patients express significantly higher levels of SGLT2 and GLUT2. The increased expression of SGLT2 in uncontrolled diabetes has practical significance, as SGLT2 inhibitors are likely to produce a greater degree of glycosuria in the presence of higher prevailing plasma glucose levels [12].

Figure 2. Mode of action of SGLT1 and SGLT2[9].



The unique mechanism of action of SGLT2 inhibitors-which does not hinge upon β-cell function or tissue insulin sensitivity-means that they can exert their antihyperglycaemic effects in combination with any other oral antidiabetic drug as well as insulin [13]. The efficacy of SGLT2 inhibitors is dependent on the amount of glucose filtered through the glomeruli. As the glomerular filtration rate (GFR) declines in renal impairment,the efficacy of the SGLT2 inhibitors decreases. Renal dysfunction is a common complication of T2DM,with 35.2% of patients having evidence of moderate to end-stage renal impairment.This implies that the therapeutic efficacy of SGLT2 inhibitors would be limited to diabetic patients with normal renal function or with mild renal impairment at best.There would be a need to monitor the renal function prior to giving this drug and during the course of therapy.The drug might even undergo a therapeutic failure with progressive deterioration of renal function during the course of treatment [14].

Pharmacological actions [6]

1. **Effect on hyperglycemia : SGLT2 inhibitors reduce both fasting and post prandial blood glucose levels significantly by their glucosuric action.They also reduce HbA1C levels by 0.3 to 0.9 %.They may not be used as first line drugs but can be used as add on therapy to oral antidiabetic drugs as well as Insulin.**

2. **Effect on weight :** In addition to improvements in glycaemic control, dapagliflozin therapy is also associated with beneficial reductions in total body weight. The glycosuria induced by dapagliflozin monotherapy is associated with a net calorie loss of approximately 200–300 kilocalories per day. List *et al*. noted that 12 weeks' monotherapy with dapagliflozin was associated with weight loss of 2.5–3.4 kg compared with weight loss of 1.2 kg and 1.7 kg in the placebo and metformin arms.[12] However there was no significant difference in weight at 24 weeks. Effect on weight could be due to loss of sodium in urine,thereby decreasing fluid retention and reducing oedema by osmotic diuresis.

3. **Effect on Blood pressure :** Dapagliflozin, as monotherapy or as an addition to metformin therapy over periods of 12–24 weeks in doses of 2.5–10 mg per day, has been noted to reduce blood

pressure. This is possibly mediated through net sodium loss. Doses of 10 mg/day reduced mean systolic blood pressure in the groups studied by 3–5 mmHg and diastolic blood pressure by approximately 2 mmHg with no apparent change in heart rate or increase in syncopal episodes.[12-14] This small decrease in blood pressure may convey additional cardiovascular benefit in addition to the effects of improvement in glycaemic control and reduced weight. This reduction in blood pressure was seen without an increased incidence of orthostatic hypotension.

4. Other effects : In a few studies, dapagliflozin treatment also increased plasma high density lipoprotein (HDL) cholesterol levels and decreased plasma triglyceride levels.This effect can also be due to better diabetic control.

5. **Cardiovascular safety : Although SGLT2 inhibiitors appear to be safe as far as cardiovascular effects are concerned, no data is yet available. Cardiovascular safety profile is being evaluated for phase III trial of Dapagliflozin and also for Canagliflozin (CANVAS study). The results are expected soon.**

Adverse reactions [6,9,10]

1. **Urinary tract infections – UTI s were significantly more in SGLT2 inhibitors group, especially in females. They were not dose dependent. They were mild to moderate and resolved with standard treatment.Only a single case of Pyelonephritis has been reported.**

2. **Genital infections – were also more in SGLT2 inhibitors treated group.Again they were more in females and were mostly vulvovaginal mycotic infections. They also responded to standard treatment.**

3. **Hypoglycemia – SGLT2 inhibitors are expected to cause less hypoglycemia as their effect is independent of Insulin release, the incidence of hypoglycemia was more as compared to placebo. Hypoglycemia was dose dependent. But it was mild to moderate. Hypoglycemia was more when they were combined with Insulin than with other OAD. However hypoglycemia is not reported to be a problem with SGLT2 inhibitors.**

4. **Cancers -** Serious but rare side effects of dapagliflozin include cancer development and hepatotoxicity. The safety data pooled from T2DM patients enrolled in phase 2b and 3 clinical trials revealed an increased incidence of bladder and breast cancer [15].

Evidence based therapeutic application of SGLT2 inhibitors

Monotherapy

Two published studies have evaluated the use of dapagliflozin as monotherapy for type 2 diabetes. In a study by List *et al* At week 12, the dapagliflozin group achieved a mean reduction in HbA_{1c} ranging from 0.55 to 0.90% when compared with Metformin which achieved a reduction of 0.73% [16]. Ferrannini *et al.* reported a mean reduction in HbA_{1c} ranging from 0.58 to 0.89% in the dapagliflozin group compared with 0.23% in the placebo group. The reduction was statistically significant in the 5 and 10 mg dapagliflozin arms [17].

Combination therapy

Wilding *et al.* randomised 71 patients receiving high-dose insulin plus insulin sensitisers to treatment with either placebo, 10 mg dapagliflozin or 20 mg dapagliflozin. All oral antidiabetic agents were continued, but baseline insulin doses were reduced by 50%. At week 12, HbA_{1c} levels in the dapagliflozin 10 mg and 20 mg groups fell by 0.70% and 0.78%, respectively, when compared with placebo [18].

In a phase III multi-centre, double-blind, parallel-group, placebo-controlled trial, Bailey *et al.*randomised 546 adults with type 2 diabetes mellitus already receiving metformin (≥1,500 mg/day) with inadequate glycaemic control (HbA_{1c} 7–10%) to treatment with one of three doses of dapagliflozin (2.5, 5 or 10 mg) or placebo. At 24 weeks, mean HbA_{1c} decreased by 0.30% in the placebo group compared with 0.67% ($p=0.0002$) in the dapagliflozin 2.5 mg group, 0.70% ($p<0.0001$) in the dapagliflozin 5 mg group and 0.84% ($p<0.0001$) in the dapagliflozin 10 mg group [19].

Only two studies examined the use of dapagliflozin in triple therapy, with insulin and no trials examined the

role of the SGLT2 receptor inhibitors in triple oral therapy [20,21].

Seven trials, published in full, assessed dapagliflozin and one assessed canagliflozin. Trial quality appeared good. Dapagliflozin 10 mg reduced HbA1c by −0.54% (weighted mean differences (WMD), 95% CI −0.67 to −0.40) compared to placebo, but there was no difference compared to glipizide. Canagliflozin reduced HbA1c slightly more than sitagliptin (up to −0.21% vs sitagliptin). Both dapagliflozin and canagliflozin led to weight loss (dapagliflozin WMD −1.81 kg (95% CI −2.04 to −1.57), canagliflozin up to −2.3 kg compared to placebo) [10].

Current status

The US Food and Drug Administration (FDA) reviewed dapagliflozin in July 2011. They felt unable to approve it without additional safety data, mainly because of concerns about bladder and breast cancer. In the study data, there were nine cases of breast cancer in the dapagliflozin groups and none in the control groups. Some of these cancers occurred not long after dapagliflozin had been started. The absence of breast cancers among the controls was considered unexpected. An analysis by the manufacturers gave a standardised incidence ratio of 1.27 (95% CI 0.58 to 2.41) but this was not sufficient to reassure the FDA committee. There were nine cases of bladder cancer in those taking dapagliflozin and only one in the control groups, though it was noted that in five cases, haematuria had been recorded before dapagliflozin was started. The FDA committee noted that the imbalance might possibly be due to detection bias. The committee voted nine to six against approval[22]. The FDA advisory panel also questioned the efficacy of the drug in renal impairment [15]. Patientswith severe renal impairment (GFR<30 ml/min/1.73 m2) were excluded from large controlled clinical trials. Hence, the efficacy and safety data could not be extracted from these patients.

Conclusion

Thus SGLT2 inhibitors i.e. Dapagliflozin and Canagliflozin represent a novel therapeutic approach to treatment in Type II Diabetes. They cause reduction in HbA1C levels as well as weight and blood pressure with less incidence of hypoglycemia.They are not first line drugs but can be used in combination with Insulin or other OADs. However there may be increased incidence of Urinary tract and genital infections. Cardiovascular and other long term safety data is yet to come.The drugs are yet to obtain FDA approval.

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